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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,402	06/12/2000	TETSUNORI FUJISAWA	2000_0562A	7196

7590 04/14/2003

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,402	FUJISAWA ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *February 27, 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-11 and 14-22* is/are pending in the application.

4a) Of the above claim(s) *8-11,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-7 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

Claims 4-11 and 14-22 are pending.

Claims 4-7 and 16-22 are rejected.

Claims 8-11, 14 and 15 are withdrawn from consideration.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 27, 2003 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 4-7 and 16-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds shown in Tables 1-3, does not reasonably provide enablement for the entire genus of structures which are potential

matrix metalloproteinase inhibitors encompassed by the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The nature of the invention is chemical, in an area where single structural substitutions may alter the function of the compound in unpredictable ways. In particular, the invention is drawn to matrix metalloproteinase inhibitors. The invention is is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claimed invention is drawn broadly to any compound which falls within the genus disclosed by the claims. The breadth of the claims is immense, where even a claim like claim 16 includes literally hundreds of millions of different compounds. This is a classic situation where these compounds are diverse, and in a poorly understood

genus. The diversity can be shown by example. In claim 16, R5, can be either an alkyl, a nitrogen containing heterocyclic radical, a cycloalkyl, and carboxy substituted lower alkyl, and alkylamino substituted lower alkyl . Each of these subgeneric limitations on R5 represents a large genus. For example, a nitrogen containing heterocyclic radical includes any heterocyclic nitrogen containing ring, which might include compounds as diverse as nucleic acid bases like adenine, chemical carcinogens like nicotine, and essential blood constituents like Heme. So even a single subgenus of a single R group in claim 16 includes compounds which are tremendously diverse, broad and poorly understood in their functionality in matrix metalloproteinases. The entire set of claims is drawn to an immense set of compounds which are diverse and poorly understood as shown by the Chemical Review article cited by Applicant, Whittaker et al (Chem. Rev. (1999) 99(9):2754) where Whittaker notes "They also investigated P1' C-alpha gem-disubstitution and found that this modification led to a loss of potency relative to the corresponding P1' isobutyl compounds with the least detrimental effect being observed for a P1' gem-cyclohexyl compound 35. However, a P1' quaternary carbon is tolerated when one of the substituents is hydroxyl as in compound 36 (see page 2754, column 2)" This statement shows that even less diverse substitutions in matrix metalloproteinases than those claimed had significantly divergent effects.

Quantity of Experimenation

The quantity of experimentation in this area is immense since there is significant variability in the activity of the compound depending upon the specific matrix metalloproteinase for which inhibition is desired, depending upon the structure of the compound and depending upon the environment in which the compound will function.

Design of matrix metalloproteinase inhibitors is an inventive, unpredictable and difficult undertaking in itself, and efficacy of each inhibitor would need to be tested or demonstrated using a variety of matrix metalloproteinases in a variety of environments ranging from in vitro to in situ to in vivo. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The prior art recognizes the extreme unpredictability in this area. In fact, Dickens et al (WO 94/02447), synthesizing extremely similiar compounds states regarding his compounds that "It has been found that such compounds have in general the sought after but unpredictable combination of desirable formulation characteristics, including water-solubility, as well as desirable activity profiles as inhibitors of MMP's (page 4)". Dickens further notes that "Unfortunately, however, the physicochemical and/or pharmacokinetic properties of the specific compounds disclosed in those publications have generally been disappointing (page 2 last sentence to page 3)". Thus, Dickens notes that 12 different patents and published patent applications synthesized particular compounds, not simply a disclosure as here of broad generic structures, and these particular compounds were unpredictable in function and unable to achieve the sought after purpose of treatment. Further evidence of the unpredictability is provided by Brenner (WO 97/05865) who notes that it is desirable to identify inhibitors, but (prior to his work) "none of the inhibitors so far identified has proven an effective therapeutic for the treatment of collagen related diseases or even an inhibitor to C-proteinase activity (page 5, lines 2-4)". Crimmin et al (U.S. Patent 5,652,262) is currently cumulative over the Dickens prior art, but Crimmin teaches similar compounds and the unpredictability of

such compounds (see column 2, lines 40-44). The entirety of the Whittaker et al Chemical Reviews article also supports a finding of unpredictability. The cited portions at page 2754 indicate that the replacements in some regions, such as P1 (which correlates to R3 of the claim) are unpredictable, noting at page 2754, column 2, that replacements at P1 resulted in loss of inhibitory activity, other replacements were unstable, and other modifications led to a loss of potency. Even the P3 modification has unpredictable effects, such as the replaced by B-amino group is indicated to have a 10-50 fold loss of activity (see page 2755, column 2). So the cited portions of the Chemical Reviews reference supports a finding of unpredictability. As shown by the art, this area is highly unpredictable and alteration of the compounds results in altered activities and altered formulation profiles which have entirely unpredictable results

Working Examples

The specification has 40 specific working examples but these examples are not representative of the full scope of the claim. As the Federal Circuit noted in In re Vaeck, 947 F.2d 488, 496 (CAFC 1991), "However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element." Here, the genus represents a relatively poorly understood set of chemical entities which are intended to function to

inhibit matrix metalloproteinases. Lastly, as noted above, the prior art of Dickens expressly refers to the current compounds as being unpredictable in activity.

Guidance in the Specification.

. While the specification provides substantial guidance on methods of making the chemical compounds and some guidance on the use of the working examples, a particular 40 or so compounds disclosed in tables 1-3 on pages 148-152 of the specification, the specification gives no guidance on the use of any compound outside of this set of compounds with regard to their function or efficacy.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability is opposed to patentability. The specification provides one with no written description or guidance that leads one to a reliable method of selecting which members of the very diverse claim will function as matrix metalloproteinases. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art recognized problems in the selection of R groups to design matrix metalloproteinases as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working examples which do not address the full scope of the claims

and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 4-7 and 16-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujisawa (JP 8-53403).

Fujisawa teaches a compound with the structure of claim 16 as shown in columns 1-12.

This compound of Fujisawa, for example compound I in columns 1 and 2, teaches a situation which anticipates claim 16 where

Claim 16 structure	Fujisawa Reference Structure
R1 - hydrogen	R1 - Hydrogen (see columns 1-12)
R2 - hydrogen	R2 - Hydrogen (see columns 1-12)
R3 - C1-4 alkyl	R3 - Shows a C1 alkyl (see structure 1)
R4 - C3-9 alkyl	Has C4 alkyl at this position (see structure 1)
N-R5-R6	R5 can be amino methyl group (see columns 1-12)
R7-8 - Hydrogen or methyl	CH_2R4 has two hydrogens and methyl
R9	R4 can be a substituted pyridine (see columns 1-12)

Fujisawa teaches that the compounds are matrix metalloproteinase inhibitors (abstract) and teaches pharmaceutically and veterinarily acceptable excipients and carriers (columns 1-12).

Allowable Subject Matter

1. The elected species, Compound 65, is novel and unobvious over the cited prior art, because none of the art teaches or suggests it's particular structure.

Response to Arguments

2. Applicant's arguments filed February 27, 2003 have been fully considered but they are not persuasive.

Applicant does not specifically traverse the rejections but simply amended the claims to remove the new matter rejection. This rejection is withdrawn. However, the remaining rejections remain applicable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

April 9, 2003